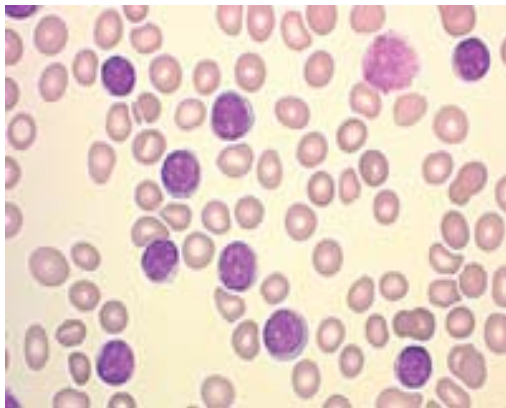


Chronic Leukemia (CLL)/MS.4th.28.02.2019

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Case 10

69 yr old man complains of fever and cervical and axillary swelling for several months with recurrent fever and productive purulent cough. P/E Splenomegaly, lymphadenopathy and pallor. Hb 10, MCV 100, Retscs 7%, Ldh 680U/ml, Blood film shown. WBC 123k, Plt 85k, DAT+3, Bilirubin 2, D 0.5



Case Ten: Diagnosis and Management

1- Decide the type of lymphocyte

2- Determine the stage

Stage IV Rai, C Binet

3- Cytogenetics

+ 12

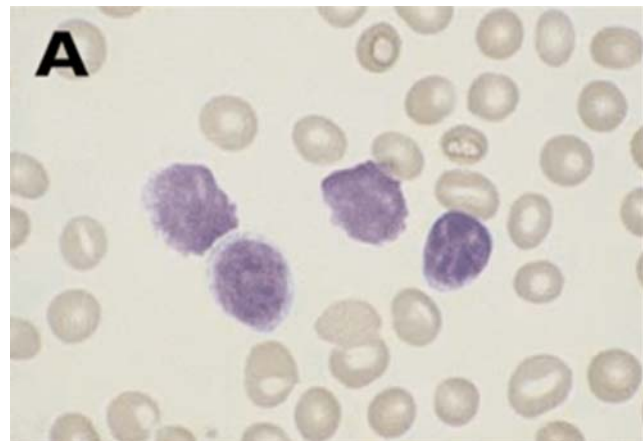
4- Decide therapy

5- Decide Prognosis

6- Determine follow-up



slg	+
CD19	++
CD20	++
CD5	+



CLL Clinical Presentation

- Lymphocytosis
 - Morphologically mature
 - Immunologically immature
 - Accumulation in PB, BM and lymphatic tissues
- Enlarged Lymph nodes
- Splenomegaly
- Hypogammaglobulinaemia

Estimating prognosis

- Clinical staging systems - Rai/Binet
 - Early - >10 years median survival
 - Intermediate - 5-7 years median survival
 - Advanced - 1-3 years median survival
- Heterogeneity of disease

Staging: Rai and Binet staging systems for CLL

Clinical staging systems for CLL

Stage

Value	Rai	Binet	Median survival
Lymphocytosis (>15,000/mm ³)	0	-	150 months (12.5 years)
Lymphocytosis plus nodal involvement	I	A <3 node groups	101-108 months (8.5-9 years)
Lymphocytosis plus organomegaly	II	B >3 node groups	60-71 months (5-6 years)
Anemia (RBCs)	III Hgb <11 g/dL	C Hgb <10 g/dL PLT <100,000/mm ³	19-24 months (1.5-2 years)
Lymphocytosis plus thrombocytopenia (platelets)	IV PLT <100,000/mm ³		

Genetic abnormalities in CLL

Genetic abnormality	Incidence (%)	Median survival (months)	Clinical correlation
13q14	55-62	133-292	Typical morphology Mutated V_H genes Stable disease
+ 12	16-30	114-122	Atypical morphology Progressive disease
del 11q23	18	79-117	Bulky lymphadenopathy Unmutated V_H genes Progressive disease Early relapse post autograft
p53 loss/mutation	7	32-47	Atypical morphology Unmutated V_H genes Advanced disease Drug resistance

Döhner H, et al. *N Engl J Med.* 2000;343:1910-1916.
 Oscier DG, et al. *Blood.* 2002;100:1177-1184.

Mutation status of VH genes

- Unmutated VH genes
 - Pregerminal centre cell
 - Rapid progression
- Mutated VH genes
 - Postgerminal centre cells
 - Slow progression
- Surrogate markers
 - ZAP 70 and CD38

CLL treatment criteria:

- Patient has symptoms
- Decline in Hb or Plt.
- Lymphadenopathy
- Hepatosplenomegaly
- Recurrent infections

CLL Treatment Options

1960s



1970s



1980s



1990s



2000



Alkylating Agents

- Chlorambucil
- Cyclophosphamide

Purine Nucleosides

- Fludarabine
- Pentostatin
- Cladribine

Purine

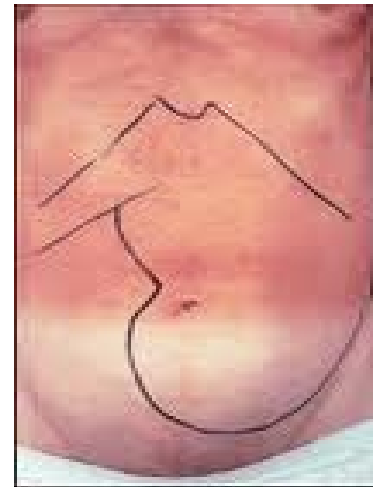
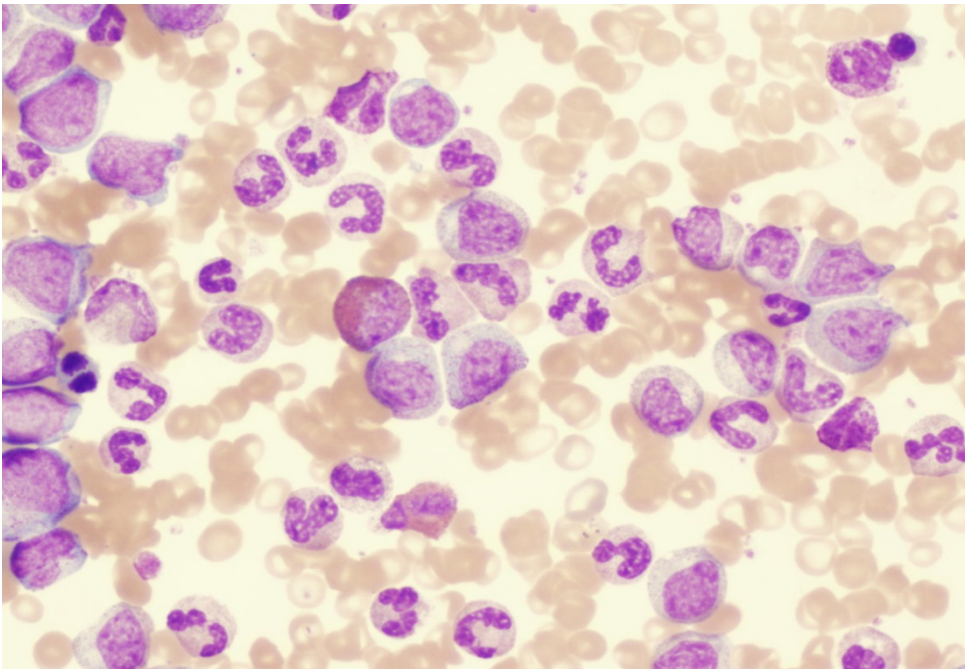
Nucleosides
Plus Alkylators

Chemoimmunotherapy

Case 10 B: CML

54 yr M, complains of L abdominal discomfort, weight loss, sweating and headaches. P/E: signs of weight loss, temp 37.3, BP 135/85. Spleen+++ . Hb 13, mcv 88, Retcs. 0.9% .Plt 800k, WBC 120k. S.uric acid 9.5.

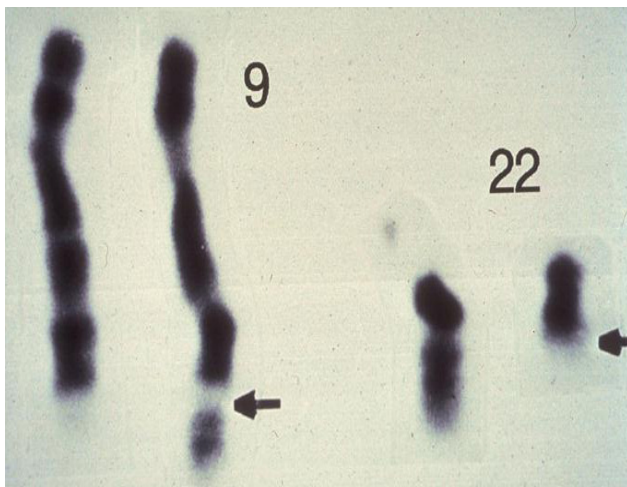
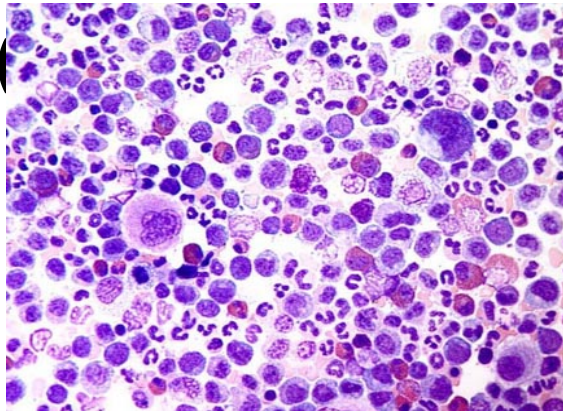
Bld film. Abd CT.



Case 10B

1- BM. 2-Karyotyping. 3- FISH.

Diagnosis: CML in Chronic Phase

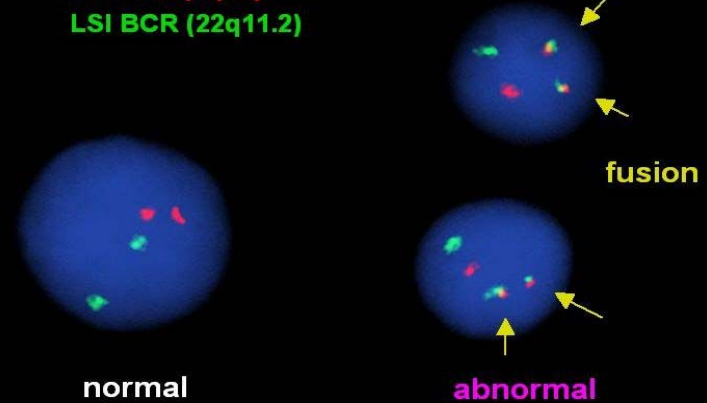


Locus specific identifier (LSI)

LSI BCR/ ABL Dual Color, Dual Fusion Probe

LSI ABL (9q34)

LSI BCR (22q11.2)



Epidemiology

- Incidence of CML is 1.5 / 100,000.
- Affects middle-aged individuals.
- CML accounts for 20% of all leukemias affecting adults.

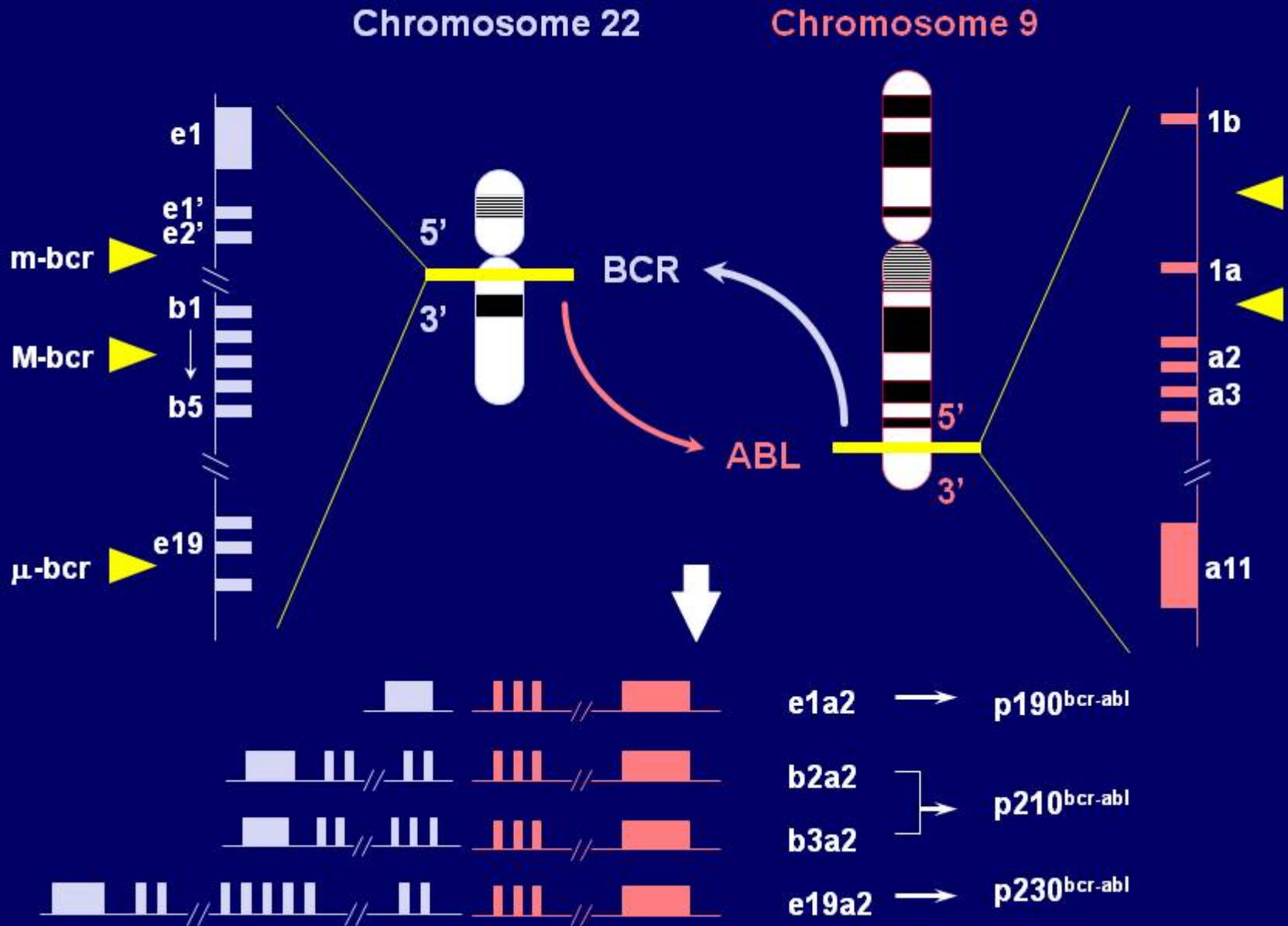
Definition

- Clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22.
- Fusion of *BCR* region on chromosome 22 with *ABL* gene from chromosome 9.
- Disease has three phases:
chronic phase, accelerated phase, and blast crisis.

Pathophysiology

- *BCR/ABL* gene product plays central role.
- Bcr/Abl fusion proteins p210^{*BCR/ABL*} and p230^{*BCR/ABL*} can transform hematopoietic progenitor cells in vitro.
- Irradiated mice injected with BM cells infected with retrovirus carrying the *BCR/ABL* gene leads to CML-like picture.

BCR-ABL: types of transcripts



Symptoms

- Insidious onset: accidental discovery
- Fatigue, malaise, weight loss
- Symptoms due to splenomegaly
 - LUQ pain, early satiety, mass
- Infections, thrombosis, bleeding.
- ?Gout
- Worsening of symptoms heralds progression (fever, weight loss, decreased response to therapy, bone pain).
- Some patients may present in the accelerated or blastic phase.

Physical Findings

- Minimal to moderate splenomegaly
- Mild hepatomegaly
- Lymphadenopathy and myeloid sarcomas rare except in terminal stages of the disease.

Hematologic Findings

- Elevated WBC, <5% blasts and <10% blasts and promyelocytes
- Elevated platelets
- Normochromic normocytic anemia
- Basophilia
- The cytogenetic hallmark of CML, found in 95% of patients, is the t(9;22)(q34;q11.2).
- Originally designated as the Philadelphia chromosome.
- All patients should have evidence of the translocation either by cytogenetics, FISH, or molecularly to make a diagnosis of CML.

Hematologic Findings

Accelerated Phase is characterized by:

- Anemia, Blood or BM basophils $\geq 20\%$, Platelet count $< 100,000/\mu\text{l}$
- Cytogenetic clonal evolution, Blood or BM blasts between 10 and 20%

Blastic Phase (Crisis)

- Acute leukemia, with blood or marrow blasts $\geq 20\%$.
- Hyposegmented neutrophils may appear (Pelger-Huet anomaly).
- Blast cells can be classified as myeloid, lymphoid, erythroid, or undifferentiated.

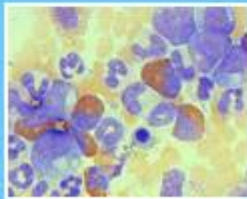
Treatment

- Aim of treatment is to reduce WBC, prevent gout and **target the molecular cause** of the disease
- The treatment has been revolutionized by imatinib mesylate, a targeted treatment.
- Stem cell transplant (SCT) is the only definitive therapy and treatment of choice in some patients.

Goals of CML therapy

Leukemia cells

$>10^{12}$



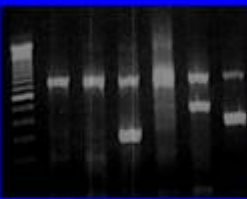
CHR

10^{10}



CCyR

10^8

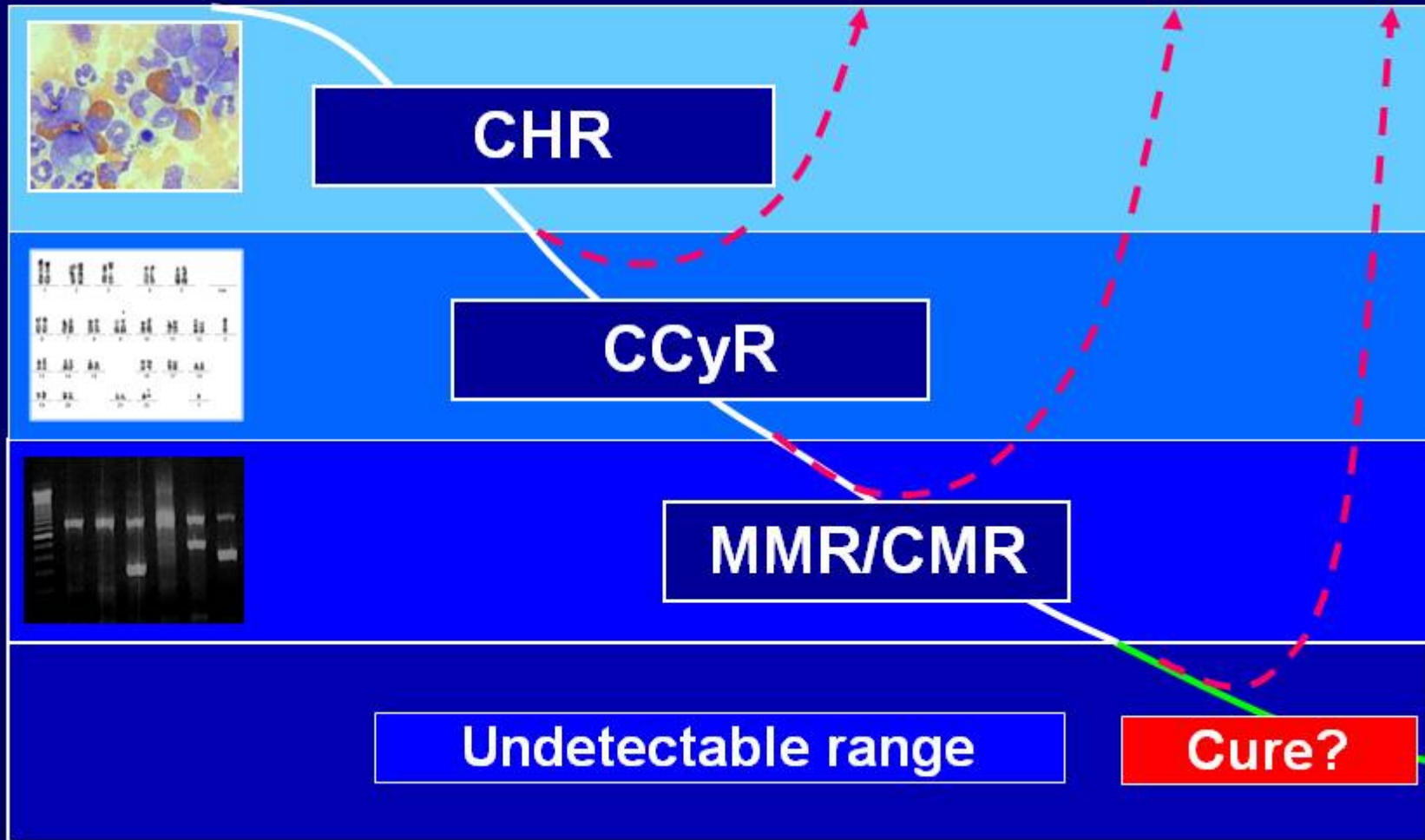


MMR/CMR

10^6

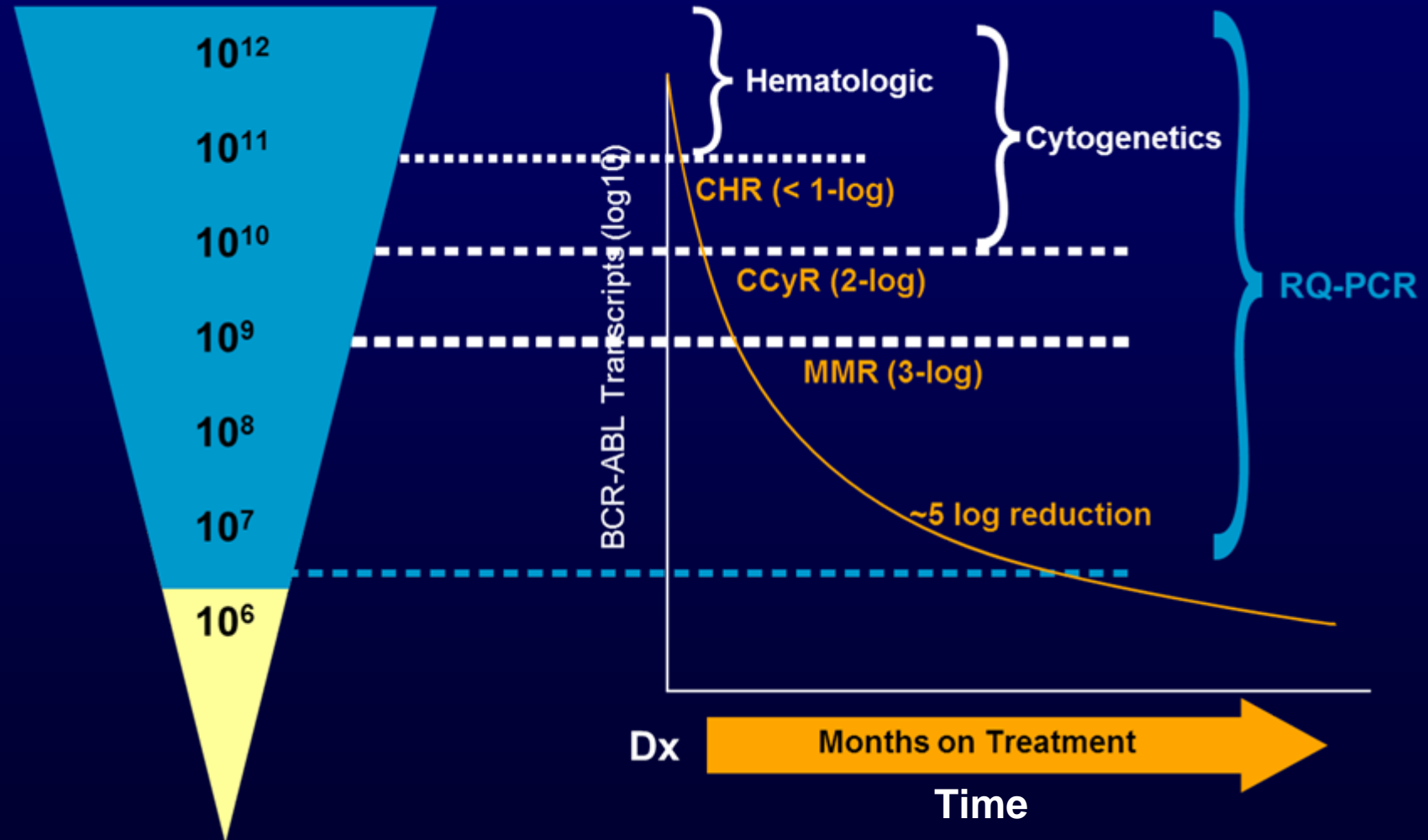
Undetectable range

Cure?



Correlation Between Response and Disease Burden: Molecular Response

Number of Leukemic Cells



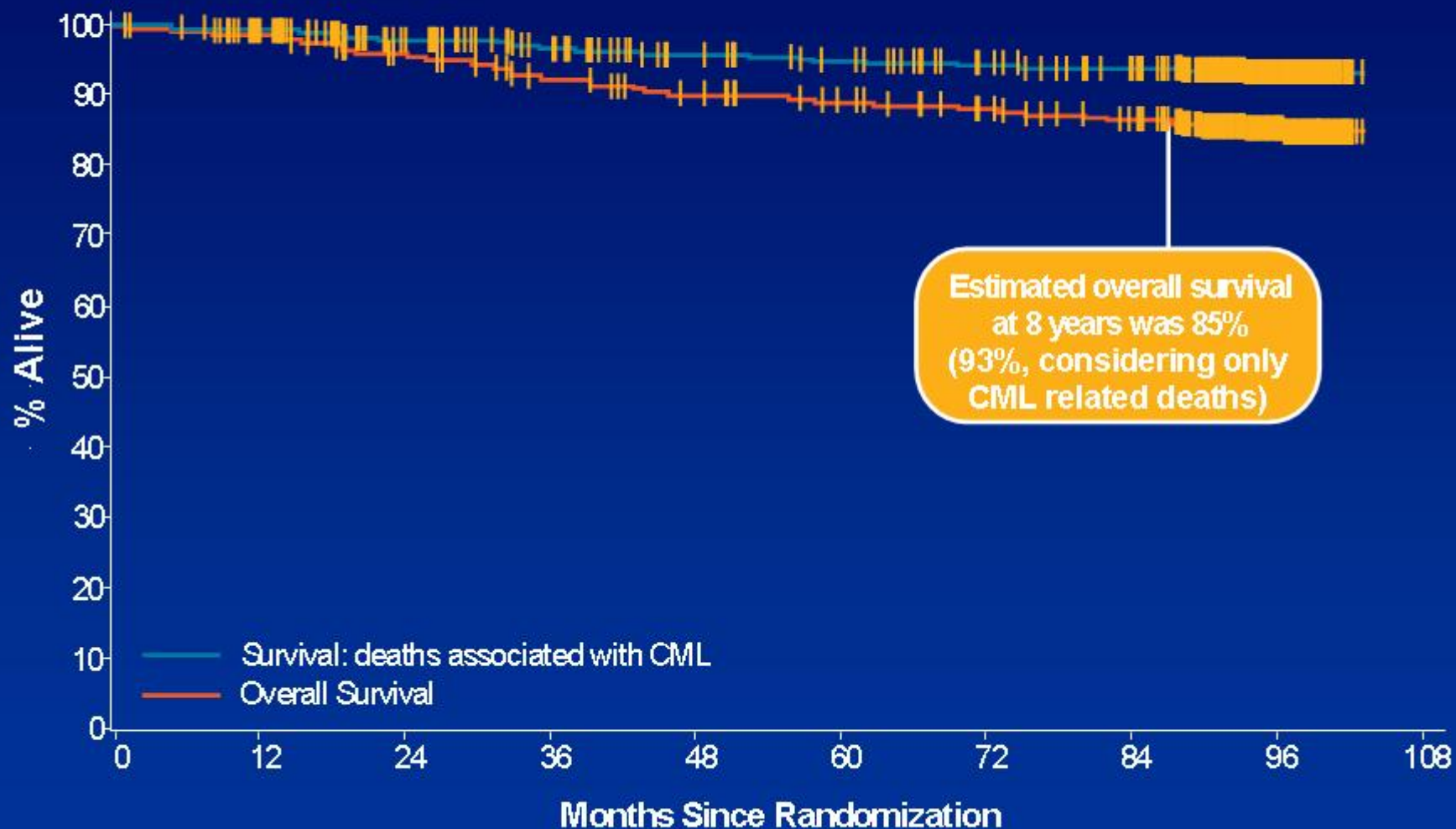
Imatinib mesylate

Competitive inhibition at the adenosine triphosphate (ATP) binding site of the Abl kinase

Rapid hematologic response.

95% of patients achieved complete hematologic remission, and 60% achieved major cytogenetic remission within few months.

Results: Overall Survival (Intent-to-Treat) – Imatinib Arm



Side effects

- The main side effects are fluid retention, nausea, muscle cramps, diarrhea, and skin rashes.
- Myelosuppression is the most common hematologic side effect.

Resistance

Mechanisms include

- Gene amplification
- **Mutations at the kinase site**
- Enhanced expression of multidrug exporter proteins
- Alternative signaling pathways functionally compensating for the imatinib-sensitive mechanisms

Other Treatment Modalities

- Alfa Interferons
- Chemotherapy (hydroxyurea, busulphan)
- Allogeneic BMT (SCT) for selected patients
- 2d generation TKI for failures or relapse or intolerance
- BMT for Crisis